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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	42

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/920,272	MILLER ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,33,41,42,49-52 and 54-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,33,41,42,49-52 and 54-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 43-47, 61-63 were canceled and claim 54 was amended in Paper No. 39, 6/9/2003. Claims 32-33, 41-42, 49-52, 54-60 are pending and under consideration.

Response to Arguments and Amendment

Applicant's arguments filed in Paper No. 39, 6/9/2003 have been fully considered but they are not persuasive. Remaining issues, and new issues, are set forth below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-33, 49-52, 54-57, 59-60 are rejected under 35 U.S.C. 102(a) as being anticipated by Sosnowski et al. (1995). Upon further consideration this rejection has been reinstated.

Sosnowski et al.(page 38, column 1, second paragraph to column 2, first paragraph) teaches the establishment in primary culture of olfactory epithelium isolated from adult mouse. Based upon immunoreactivity (page 45, column 1, fourth paragraph) to antibodies specific for intermediate filament proteins, the cells present in cultures were identified as neurons, glia or epithelial cells. The claims are directed to compositions of cells comprising neural stem cells

with these properties. The claimed cellular compositions comprise multipotent stem cells with the recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Additionally, the composition of cells as taught by Sosnowski would be inherent to comprise cells that are capable of forming non-adherent clusters. It is an inherent property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the inherent properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, claims 50-52, 54-57, 59-60, are anticipated.

Claim 49 is a product by process claim, and claims 32-33, 56-57, 59-60 depend from claim 49. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). In addition, it has been established by the courts that when a product (i.e. mammalian neural stem cells) inherently possesses a characteristic of that product (see e.g. *Ex parte Gray*, 10 USPQ2D, 1922; In re Best, 195 USPQ 430), that ""[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re*

Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983). In the instant case, the claimed cellular compositions comprise multipotent stem cells with several recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Furthermore, it is an inherent property of mammalian neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner, therefore claims 32-33, 49, 56-57, 59-60 are anticipated.

Claims 32-33, 49-52, 54-57, 59-60 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,318,907 (Ronnette et al.). Upon further consideration this rejection has been reinstated.

Ronnette et al. (column 6 line 58 to column 7 line 46) discloses the isolation of cells from the olfactory epithelium of neonatal rats, and their establishment in primary culture. The presence of both neurons and glial cells is demonstrated through immunoreactivity with antibodies specific for neurons (anti-neuron-specific enolase) and glial cells (anti-glial fibrillary

acidic protein) (column 8, lines 34-47). The development in culture of neuronal cells indicates the presence of neural stem cells and neural progenitor cells. The instant claims are directed to compositions of cells comprising neural stem cells with these properties. The claimed cellular compositions comprise multipotent stem cells with several recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. In the '907 patent, the presence in culture of glial cells, together with the presence of neurons meets the limitations for a multipotent cell. Thus the cells disclosed in the '907 patent meet the limitations set forth in the claims for an isolated composition of neural stem cells of a mammal (see column 2, lines 41-45). Additionally, the composition of cells as disclosed in the '907 patent would be inherent to comprise cells which are capable of forming non-adherent clusters. It is an inherent property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the inherent properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, the claims are anticipated. Furthermore, it would be an inherent property of the composition of cells as disclosed in the '907 patent to comprise cells which are capable of forming non-adherent clusters. It is an inherent property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the inherent properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, claims 50-52, 54-57, 59-60, are anticipated.

Claim 49 is a product by process claim, and claims 32-33, 56-57, 59-60 depend from claim 49. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In addition, it has been established by the courts that when a product (i.e. mammalian neural stem cells) inherently possesses a characteristic of that product (see e.g. *Ex parte Gray*, 10 USPQ2D, 1922; In re Best, 195 USPQ 430), that ""[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983). In the instant case, the claimed cellular compositions comprise multipotent stem cells with several recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Furthermore, it is an inherent property of mammalian neural stem cells that they are GAD positive, are capable of differentiating into

dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner, therefore claims 32-33, 56-57, 59-60 are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32-33, 41-42, 49-52, 54-60 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al (1995), in view of U.S. Patent No. 5,824,489 (Anderson et al.) for reasons of record set forth in Paper No. 37, 12/4/2002.

The rejection of record set forth that Sosnowski et al.(page 38, column 1, second paragraph to column 2, first paragraph) teaches a primary culture of olfactory epithelium isolated from adult mouse. Based upon immunoreactivity (page 45, column 1, fourth paragraph) to antibodies specific for intermediate filament proteins, the cells present in cultures were identified

as neurons, glia or epithelial cells. Thus, Sosnowski teaches progenitor cells isolated from peripheral tissue, in this instance olfactory epithelium, of a postnatal mammal. The cells isolated by Sosnowski et al. have been shown to be multipotent, due to the presence in culture of several cell types. Sosnowski et al. teaches that the cultures established from regenerating olfactory tissue after chemical insult exhibited a range of neuronal yields (page 47, column 1, third paragraph). Cellular components of the cultures produced by Sosnowski et al. tested positive for keratin, as well as 200 kD and 160 kD neurofilament proteins, indicating the establishment of mixed olfactory epithelial cultures containing olfactory neurons (page 46, column 1, first paragraph). The cells comprising the composition of Sosnowski et al. were isolated from peripheral tissue, i.e. olfactory epithelium, in a fashion similar to the cells claimed in the instant application. The cells in the composition taught by Sosnowski et al. differentiate to produce neuronal cells, as do the cells of the instant application. The cells in the composition of Sosnowski et al. can be transplanted into the CNS of a mammal, as can the cells of the instant application.

The cells of Sosnowski et al. do not express nestin or are transfected with a heterologous gene. The '489 patent discloses multipotent neural stem cells can be derived from neural epithelial tissue from the brain and/or spinal cord of the adult central nervous system or neural epithelial tissue which may be present in tissues comprising the peripheral nervous system. In addition, the '489 patent discloses that such multipotent neural stem cells may be derived from other tissues such as lung, bone and the like (column 5, lines 40-47). The cells disclosed in the '489 patent express nestin (column 6, lines 1-5). The '489 patent discloses that the cells may be transfected with a vector (column 3, lines 59-63) and that mammalian neural crest stem cells may

be isolated from human tissues (column 4, lines 54-58). Therefore it would have been obvious to one of skill in the art at the time the invention was made to make a population of neural stem cells from a mammal, including humans, from peripheral tissue, wherein the neural stem cell expresses nestin. The motivation is provided in the '489 patent which discloses that the ability to isolate and grow mammalian neural crest stem cells in vitro allows for the possibility of using said stem cells to treat peripheral neurological disorders in mammals, particularly humans.

Applicant argues that there was no motivation to combine the teachings of Sosnowski and Anderson because one would not be motivated to look for the nestin-positive cells of the '489 patent in the cells of Sosnowski. However, the '489 patent discloses that multipotent neural stem cells may be derived from various tissues, including, inter alia the peripheral nervous system (column 5, lines 39-47). The '489 patent further discloses that the multipotent neural stem cells may also be characterized by the expression of nestin (column 6, lines 1-5). The disclosure of the '489 patent thus teaches that nestin positive multipotent neural stem cells may be derived from tissues other than neural crest, specifically from the peripheral nervous system. The Sosnowski reference teaches multipotent cells derived from the peripheral tissues of a mammal, thus it would have been obvious at the time the invention was made to produce the nestin positive multipotent neural stem cells as taught in the '489 patent by using the peripheral olfactory tissue as taught by the Sosnowski reference, since the Sosnowski reference teaches the unique capacity of the olfactory epithelium to remain mitotically active throughout a mammals life, and that the multipotent cells derived from olfactory epithelium could be harvested, grown and autotransplanted.

Applicant further argues that the combination of the Sosnowski reference with the '489 patent fails to teach every element of the claims because they do not teach non-adherent clusters of stem cells, they do not teach that the stem cells are capable of differentiating into dopaminergic neurons, and they do not teach that the stem cells are GAD positive. Applicant additionally argues that the combination of the Sosnowski reference with the '489 patent fails to teach every element of the claims because they do not teach cells which are self-renewing in an EGF independent manner. However, the claims are directed to compositions of cells comprising neural stem cells with these properties. The claimed cellular compositions comprise multipotent stem cells with the recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Additionally, the composition of cells as taught by Sosnowski in view of the '489 patent would be expected to comprise cells which are capable of forming non-adherent clusters. It is an expected property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the expected properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, the claims are unpatentable.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
August 22, 2003

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